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Combined use of several vector control tools for the control of dengue in Malaysia

Submission date
14/04/2020

Recruitment status
No longer recruiting

Registration date
17/04/2020

Overall study status
Completed

Last Edited
19/05/2025

Condition category
Infections and Infestations

[_] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Dengue is an infectious disease transmitted by mosquitoes. Infection by dengue virus causes a wide range of illness from asymptomatic or mild febrile manifestation to life-threatening conditions such as dengue haemorrhagic fever. It is estimated that over 3.5 billion people around the world are at risk of infection: 390 million infections occur per year and around 500.000 people develop severe dengue requiring hospitalization. In addition to the treatment expenses, dengue fever has additional costs due to vector control related activities.
In Malaysia, Dengue is endemic, putting all 27.5 million inhabitants at permanent risk of infection. In 2009, dengue-related medical costs and productivity loss were over US$102 million. In addition, the government spent US$73.5 million on its national dengue vector control program. Between 2001 and 2013, about 7% to 9% of the population were infected by dengue each year.
Currently, there is no consensus regarding the type of vector control approach that can have the largest impact on the number of dengue cases. The World Health Organization recommends integrated vector management (IVM) in order to make vector control activities more efficient, cost-effective, ecologically sound and sustainable. Vector control interventions on different stages of the mosquito's life cycle together with active public engagement activities are recommended.
The aim of this study is to evaluate the effectiveness of an IVM approach on the incidence of dengue in selected areas in Malaysia.
Malaysia has a great dengue surveillance system where health practitioners are required by law to report suspected cases of dengue to the Ministry of Health within 24 hours. This triggers a chain of events including fogging in the area around the zone of the reported case. The existence of appropriate infrastructure (expertise in vector control management, strong social mobilization capacities, surveillance systems), and high dengue endemicity, are reasons for carrying out this study in Malaysia. In addition, Malaysian public health authorities, in particular, the Ministry of Health acknowledged their interest in the proposed study and the potential of its scaling up based on the results.

Who can participate?
Low – medium income residential areas in the Federal territory of Kuala Lumpur and Putrajaya

What does the study involve?
The study involves integrated vector management that combines targeted outdoor residual spraying (TORS), larviciding using auto-dissemination devices (ADDs) and public engagement activities. All outer walls in all floors covered or partly covered will be sprayed with insecticide once every 4 months for a period of 2 years. ADDs are a unique combination of larvicide and a slow-killing biological adulticide with extremely low dosage developed for outdoor use. They will be placed on the ground floor, 1st, 2nd and last floors and another 2 to 6 will be distributed evenly on other floors whichever necessary. Community engagement will be maintained throughout the study period. The first step consists of an appointment with the community leader in each area through phone/e-mail/WhatsApp in order to plan a briefing face-to-face meeting. The objectives, procedure and timelines of the study will be presented to community leaders followed by a question/answer session. A second meeting involving the population can be organized upon the community leader request. Banners, posters, and announcement brochures will be distributed to explain the objectives of the study and the role of the community during and following the deployment of the intervention. The mosquito population will be monitored using conventional existing methods such as ovitraps. The number of dengue cases in each area will be provided by the national dengue surveillance system, e-Dengue. The effect of the intervention on the incidence of dengue will be calculated.

What are the possible benefits and risks of participating?
The combination of these two vector control tools together with active public engagement activities present a new chapter in vector control. The current package targets all stages of the mosquito's life-cycle and complements it by involving the population to make people better aware of the problems and solutions causing a behavioral change. It is expected that preventive action, as proposed in this study, instead of routine reactive actions will not only result in fewer cases of dengue but will be economically beneficial as well. Relatively simple maintenance of both vector control methods would lower the number of dengue cases, increasing the overall health, productivity and lowers medical costs related to dengue. The products used for the purpose of this trial have been found to be safe. There is no risk of harm for participants.

Where is the study run from?
Low – medium income residential areas in the Federal territory of Kuala Lumpur and Putrajaya (Malaysia)

When is the study starting and how long is it expected to run for?
January 2018 to August 2022

Who is funding the study?
1. Ministry of Health (Malaysia)
2. Innovative Vector Control Consortium (IVCC) (UK)
3. Bayer SAS (France)
4. In2Care (Netherlands)
5. Finovi foundation (France)

Who is the main contact?
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Contact information

Type(s)
Public

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Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
Study Protocol_Version 3, dated 10/10/2019

Study information

Scientific Title
Effectiveness of novel tools for integrated vector control management on the incidence of dengue in Malaysia: a cluster randomized controlled trial

Acronym
iDEM: intervention for Dengue Epidemiology in Malaysia

Study objectives
Co-application of several new vector control techniques together with community engagement would further enhance the vector control efficacy to ensure favourable outcomes i.e. decrease the incidence of dengue. Moreover, using an innovative combination of multiple insecticides (with different modes of action) in the same program is expected to have significant benefits for insecticide resistance management.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 05/12/2019, Medical Research & Ethics Committee, Kementerian Kesihatan Malaysia (d/a Kompleks Institut Kesihatan Negara, Blok A, No 1, Jalan Setia Murni U13/52, Seksyen U13, Bandar Setia Alam, 40170 Shah Alam, Selangor; +60 (0)3 3362 8888/8205; no email address provided), ref: NMRR-18-636-39710 (IIR)

Study design
Cluster randomized controlled trial

Primary study design
Interventional

Study type(s)
Prevention

Health condition(s) or problem(s) studied
Dengue

Interventions
The sample size determination was based on an adapted version of the bootstrap approach proposed by Kleinman K and Huang SS [Kleinman 2016] for cluster randomized trials. Localities in the catchment area that fulfilled the eligibility criteria are the sampling frames for the intervention and control arms and were randomly allocated between the arms. The random allocation of the localities to the control or the intervention arm (1:1 ratio) was carried out using the plan procedure of SAS software, version 9.4 (Copyright (c) 2002-2012 by SAS Institute Inc., Cary, NC, USA) by a statistician of the Service of Biostatistics of Hospices Civils de Lyon, France. The code written by a first statistician was double-checked by a second statistician in regard to the conformity to the randomization protocol.

The random allocation was stratified on the level of the localities (low or medium) because the dengue incidence rate is different between the two strata. In each stratum, the localities were randomly numbered and block randomization was carried out with block sizes of 10 and 16 in order to allocate the localities to the arm 1 (intervention) or 2 (control). Then the list of localities in each arm was saved in a text file and transmitted to the investigators. Randomization has

been carried out following the approval of the protocol by the IMR research committee and district/ state health office. The study population include all household members living in high-rise buildings in both intervention and control areas.

Overall, 280 clusters will be randomly allocated in a 1:1 ratio, in an unblinded manner, to receive either the proactive IVM approach or the standard vector control activities. The sample size determination is based on an adapted version of the bootstrap approach for cluster randomized trials. If it is assumed that the intervention reduces the incidence by 33% (the mean incidence rate across localities was 0.34% per year, range: 0 to 4% per year), the inclusion of the 280 eligible localities (140 per arm) will allow reaching a power of 85% for a two-sided significance level of 5%.

In clusters randomized to the intervention arm, the intervention will consist of an integrated vector control management that combines: targeted outdoor residual spraying (TORS) by K-Othrine Polyzone, deployment of auto-dissemination devices (ADDs) and public engagement activities. K-Othrine Polyzone contains deltamethrin as its active ingredient (62.5 G/L). All outer walls in all floors covered or partly covered will be sprayed. TORS will be renewed every 4 months in all intervention clusters. ADDs will be distributed in the intervention areas by vector control personnel. One device is needed for each 400 square m. The suitable number of ADDs per location depends on site characteristics of each block, for example for 15-floor building with 540 houses will need 50 ADDs. ADDs will be placed on the grand floor, 1st, 2nd and last floors and another 2 to 6 will be distributed evenly on other floors whichever necessary. ADDs will be serviced every 8 weeks to assess the average evaporation speed and hence when the water needs to be replenished. Public engagement will be started at the time of baseline data collection and maintained throughout the study period by a team of five persons specially trained in community engagement management. The first step consists of having an appointment with the community leader in each cluster through phone/e-mail/WhatsApp and using a standard script in order to plan a briefing face-to-face meeting. The objectives, procedure and timelines of the study will be presented to community leaders followed by a question/answer session. The consent form will be subsequently signed by the community leaders if they accept to participate. Information on demographic and architectural characteristics (number of buildings, number of floors per building, number of units per floor, total number of occupants) of the cluster will be collected after the consent form was signed. A second meeting involving the population can be organized upon the community leader request. A liaison officer will be assigned to each cluster for regular contact with the community leader. Banners, posters, and announcement brochures will be distributed to explain the objectives of the study and the role of the community during and following the deployment of the intervention. Social and media engagement will be carried out following the obtention of approval.

Clusters randomized to the control arm will follow the routine vector control already in place in Malaysia as in Standard Operational Procedures and guidelines given by the Malaysian Ministry of Health. Current vector control methods used in Malaysia are: space spray and Aedes breeding source elimination indoor and outdoor of the residential areas following the occurrence of a dengue outbreak.

The intervention will last for 2 years and will include three rounds of TORS spraying (overall 6 during two years), deployment of ADDs and community engagement throughout the study period.

There is no follow-up planned. However, the number of dengue cases in both intervention and control areas can be obtained from the national e-Dengue system up to one year after the end of the intervention.

The primary outcome measure is the estimated dengue incidence rate in control and treatment areas. The numerator (i.e. number of new dengue cases) will be obtained from the national eDengue system. The denominator (i.e. total number of individuals living in each cluster) will be obtained during the community engagement meetings. In each cluster, the estimate of the incidence rate of dengue will be estimated as the ratio of the number of dengue cases registered during the follow-up, divided by the number of person-years. A negative binomial regression model will be used to estimate the incidence rate of dengue in each arm with its 95% confidence interval, and to quantify the effect of the intervention on the incidence rate taking into account over-dispersion. The effect of the intervention will be quantified by a rate ratio corresponding to the exponential of the regression coefficient estimate associated to the intervention. The bounds of the 95% confidence interval of the rate ratio will be equal to the exponential of the bounds of the 95% confidence interval of the regression coefficient.

The secondary outcome measure will be to assess the impact of the treatment on the Aedes population. This includes evaluation of ovitrap index (OI) and larval count per trap. OI is estimated as the percentage of the number of positive ovitraps to the number of ovitraps recovered. OI will be estimated over the baseline and intervention period in sites selected for entomological monitoring. To quantify the effect of the interventions on the risk of positivity, a modified ordinary least squares regression model using a robust standard error estimator will be implemented. The analysis will be adjusted on the baseline measurement of the outcome. Using this model, the effect of the interventions will be quantified by the estimation of a difference of risk with its 95% confidence interval. This analysis will be carried out globally and for each of the two species of mosquito separately.

Larval count per trap is the total number of larvae recovered in positive ovitraps. Larval count per trap will be estimated in the sites selected for entomological monitoring over the baseline and intervention period. A negative binomial regression will be used with the number of larvae as the response variable. The analysis will be adjusted on the baseline measurement of the outcome. Using this model, the effect of interventions will be quantified by the estimation of a ratio of means with its 95% confidence interval. This analysis will be carried out globally and for each of the two species of mosquito separately if possible.

The trial will be governed by a consortium composed of academic/private partnership with skills and knowledge in the epidemiology of infectious disease in particular vector-borne diseases, entomology, new vector control technologies, policy makers and statistics as follows: The Institute for Medical Research (IMR, Malaysia), Ministry of Health Malaysia, Claude Bernard University (Lyon-1) and Hospices Civils de Lyon-France, Innovative Vector Control Consortium (IVCC), London School of Hygiene and Tropical Medicine (LSHTM), In2Care and Bayer SAS.

Intervention Type
Mixed

Primary outcome(s)
Dengue incidence rate estimates obtained from the national eDengue system at the end of the intervention, year 2

Key secondary outcome(s))

1. Ovitrap index estimated as the percentage of the number of positive ovitraps to the number of ovitraps recovered at the end of baseline data collection (08/02/2020) and at the end of the intervention, year 2
2. Larval count per trap estimated as the total number of larvae recovered in positive ovitraps at the end of baseline data collection (08/02/2020) and at the end of the intervention, year 2

Completion date
31/08/2022

Eligibility

Key inclusion criteria
This is a cluster randomized trial that does not involve the direct participation of individuals. Low and medium level localities in the Federal Territory of Kuala Lumpur and Putrajaya, Malaysia with 800 to 8000 inhabitants and with recurrent dengue outbreaks reported from 2015 to 2018 were eligible to be included in the trial.

Participant type(s)
Other

Healthy volunteers allowed
No

Age group
All

Sex
All

Key exclusion criteria
1. Localities within 1 km radius from Wolbachia study sites and other study sites registered with MOH Malaysia
2. Localities listed as school and universities hostel, police and fire department training centre and construction sites

Date of first enrolment
10/02/2020

Date of final enrolment
10/02/2022

Locations

Countries of recruitment
Malaysia

Study participating centre

Medical Entomology Unit, Institute for Medical Research
Jalan Pahang
Kuala Lumpur
Malaysia
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Study participating centre
Ministry of Health
Kompleks E, Blok E1, E3, E6, E7 & E10, Pusat Pentadbiran Kerajaan Persekutuan
Putrajaya
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62590, 62000

Sponsor information

Organisation
Institute for Medical Research

ROR
https://ror.org/03bpc5f92

Funder(s)

Funder type
Research organisation

Funder Name
Innovative Vector Control Consortium (IVCC)

Funder Name
In2Care B.V

Funder Name
Fondation Innovations en Infectiologie (Finovi)

Funder Name

National Institute of of Health Malaysia, Ministry of Health

Results and Publications

Individual participant data (IPD) sharing plan

Entomological data can be available at the end of the trial. The Malaysian Ministry of Health is the only owner of individual data of dengue cases. They will perform descriptive statistical analysis for the purpose of the study. The researchers will have the number of dengue cases in each cluster. This data can be available following approval of the Ministry of Health without naming the clusters.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		06/04/2022	09/07/2024	Yes	No
Results article		12/05/2025	19/05/2025	Yes	No
Protocol article		30/05/2021	01/06/2021	Yes	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes